IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Waldmann, et al.
Serial No.:	10/615,718
Filed:	July 9, 2003
For:	Therapeutic Antibodies with Reduced Side Effect
Group:	1643
Examiner:	Blanchard

Commissioner for Patents
Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

INTRODUCTORY REMARKS

This is an Appeal from the Final Rejection mailed March 6, 2009.

Real Party in Interest

The real party in interest is Isis Innovation Ltd., which is owned by Oxford University of Oxford, United Kingdom.

Related Appeals and Interferences

There are no related appeals, interferences, or judicial proceedings with respect to the above-identified application. There are no continuing applications of the above-identified application. There is a related patent, U.S. Patent No. 7,465,790, which issued on December 16, 2008, and a related application, i.e., application Serial No. 12/316,621, filed December 15, 2008.

Status of Claims

Claims 1, 6-10, 12-15, and 17 stand finally rejected, and are before the Board on

Appeal. These claims are listed in the Appendix-Claims on Appeal attached hereto. Claims 2-5 and 11 have been cancelled, and Claim 16 has been withdrawn from consideration.

Status of Amendments

No Amendments after the Final Rejection were filed.

Summary of Claimed Subject Matter

The present invention, as defined broadly in Claim 1, is directed to a pharmaceutical. The pharmaceutical comprises a therapeutic antibody and a pharmaceutical carrier. The therapeutic antibody binds to a therapeutic target, and is modified with a peptide that reduces binding of the antibody to the therapeutic target. The modified antibody is effective for reducing side effects caused by the antibody and for producing a therapeutic effect by binding to a therapeutic target. The antibody includes an antibody combining site that binds to the therapeutic target, and the peptide is bound to the antibody combining site of the antibody.

Grounds of Rejection to Be Reviewed

1. The rejection of Claims 1, 6, 9, 10, and 17 under 35 U.S.C. 102(b) as being anticipated by Hale, Immunotechnology, Vol. 1, pgs. 175-187.

2. The rejection of Claims 1, 6-10, 12-15, and 17 under 35 U.S.C. 112, first paragraph, for failing to comply with the written description requirement in that the claims contain subject matter which does not convey to one skilled in the art that the inventors had possession of the claimed invention.

3. The rejection of Claims 1, 6-10, 12-15, and 17 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical

composition comprising CAMPATH-1H (humanized anti-CD52 antibody), modified by linkage to a CD52 mimotope selected from QTSSPSAD and QTSAAAVD, does not reasonably provide enablement for all other therapeutic proteins and therapeutic antibodies modified (i.e., bound or linked) with just any other peptide or molecule (i.e., compound) wherein the therapeutic protein or therapeutic antibody has reduced side effects and produces a therapeutic effect by binding to the therapeutic target.

Argument

The Rejection of Claims 1, 6, 9, 10 and 17 under 35 U.S.C. 102(b)

In the Final Rejection, from Page 10, line 15 to Page 12, line 3, the Examiner states that the fact that Applicants' claims recite a purpose of a process does not distinguish the claimed pharmaceutical comprising a therapeutic antibody bound to a peptide that inhibits binding of the antibody to a therapeutic target, from the anti-CD52 humanized antibody, reversibly bound by a CD52 mimotope that inhibits binding of CAMPATH-1H to human lymphocytes expressing CD52. The Examiner also states that Hale discloses the antibody in various buffers, which reasonably can be interpreted as pharmaceutically acceptable carriers.

The present invention, as defined broadly in Claim 1, is directed to a pharmaceutical comprising a therapeutic antibody that binds to a therapeutic target. The antibody has been modified with a peptide that reduces binding of the antibody to the therapeutic target. The modified antibody is effective for reducing side effects caused by the antibody, and produces a therapeutic effect by binding to the therapeutic target. The antibody includes an antibody combining site that binds to the therapeutic target. The peptide is bound to the antibody combining site of the antibody. The

pharmaceutical also includes a pharmaceutical carrier.

Hale discloses the testing of the binding of Campath antibodies to various CD52 mimotopes. In the experiments of Hale, however, the Campath antibodies were not modified.

More particularly, Hale discloses various assays, such as ELISA assays and inhibition assays, to determine the binding of unmodified Campath antibodies to various mimotopes of the CD52 epitope to which Campath binds. (See Page 177, column 1, line 21 to Page 178, column 2, line 27) Such assays were conducted in order to characterize more precisely the epitope which is recognized by Campath antibodies, and to construct analogues of the epitope that would be useful in assays and for purifying unmodified Campath antibodies, as well as for further study of the antibody-antigen binding site.

Figure 8 of Hale (Page 183, column 1) shows that two of the mimotopes tested by Hale inhibited binding of the unmodified Campath antibody to human lymphocytes. Hale, however, does not disclose or even remotely suggest to one of ordinary skill in the art that the Campath antibody may be modified with such mimotopes in order to provide a modified antibody.

Hale is directed solely to studying the binding of unmodified Campath antibodies to CD52 mimotopes in order to aid in developing assays and in purifying Campath antibodies, as well as studying the antibody-antigen interaction between Campath antibodies and the CD52 epitope recognized by Campath, or mimotopes thereof.

In contrast to Hale, Applicants modify an antibody with a peptide in order to inhibit binding of the antibody to a therapeutic target, and to reduce the immune

response against the antibody. Although binding of the antibody to a therapeutic target is inhibited, there is some binding of the antibody to the therapeutic target, and a therapeutic effect is produced. Thus, the modified antibody provides a therapeutic effect while an immune response to the antibody is reduced. Hale does not disclose, nor does Hale even remotely suggest to one of ordinary skill in the art such a modified antibody, as claimed by Applicants. Therefore, Hale does not anticipate Applicants' claimed antibody nor does Hale render Applicants' claimed antibody obvious to one of ordinary skill in the art. It is therefore respectfully requested that the rejection under 35 U.S.C. 102(b) be reversed.

The Rejection of Claims 1, 6-10, 12-15, and 17 Under 35 U.S.C. 112, First Paragraph, As Failing to Comply with the Written Description Requirement in that the Claims Contain Subject Matter, Which Does Not Convey to One Skilled in the Art that the Inventors Had Possession of the Claimed Invention.

The Examiner has taken the position that the written description of the application only reasonably conveys a therapeutic humanized anti-CD52 antibody, Campath-1H, modified by linking two different CD52 mimotopes, in which the antibody-mimotope conjugate reduced the immune response (i.e., cytokine release) and had a therapeutic effect by binding CD52.

Contrary to the Examiner's allegations, the specification describes what the invention is as well as what the invention does. The present invention is directed to a pharmaceutical that comprises a therapeutic antibody that includes an antibody combining site, and is modified with a peptide that is bound to the antibody combining site. Those skilled in the art understand readily that different antibodies will have

different antibody combining sites, and that the location of the antibody combining site of an antibody can be determined by routine experimentation. Once the antibody combining site has been determined, one can modify the antibody by binding a peptide to the antibody combining site of the antibody by means known to those skilled in the art. In other words, once one skilled in the art has read what the modified antibody includes, one skilled in the art would be able to make the modified antibody by standard techniques known to those skilled in the art. Once the modified antibody is constructed, one skilled in the art would be able to determine through routine experimentation whether the peptide reduced binding of the antibody to the therapeutic target and reduced the immune response against the antibody. Therefore, for the above reasons and others, the specification provides a written description of the invention, and it is therefore respectfully requested that the rejection under 35 U.S.C. 112, first paragraph, be reversed.

The Rejection of Claims 1, 6-10 12-15, and 17 Under 35 U.S.C. 112, First Paragraph, for Failing to Provide an Enabling Disclosure.

The Examiner has taken the position that the specification reasonably does not provide enablement for all modified therapeutic proteins and modified therapeutic antibodies other than CAMPATH-1H modified by linkage to a CD52 mimotope selected from QTSSPSAD and QTSAAAVD.

As noted hereinabove, the Examiner has admitted that the specification is enabling for a pharmaceutical composition comprising Campath-1H modified by linkage to a CD52 mimotope selected from QTSSPSAD and QTSAAAVD.

The Examiner has misunderstood Applicants' previous arguments in that the

Examiner believes that such arguments were directed to showing that one skilled in the art would be able to make and test the invention, as opposed to make and use. What Applicants assert is that one skilled in the art would know how to modify antibodies other than Campath-1H in accordance with the present invention. One skilled in the art would be able, by routine experimentation, to bind peptides to antibody combining sites of other antibodies to provide modified antibodies. Once one has made a modified antibody, then one can test the modified antibody by techniques known to those skilled in the art, in order to determine whether binding to the therapeutic target has been reduced. Once one has tested and determined that binding of the modified antibody to the therapeutic target has been reduced, one skilled in the art then would know that such modified antibody can be used to provide a therapeutic effect while providing a reduced antibody response against the modified antibody, and therefore one skilled in the art is enabled to use the modified antibody. Thus, Applicants have enabled one skilled in the art to make and use the invention, and therefore the claims are patentable under 35 U.S.C. 112, first paragraph.

The Examiner also states that even minor changes in an epitope sequence may affect the antigen binding-function of the antibody.

Applicants assert that such statement has no relevance with respect to enablement. The mere fact that the amino acid sequence of an epitope has been altered does not mean that an antibody cannot bind to an unmodified epitope. The Examiner appears to be stating that just because an antibody may not be able to bind to a modified epitope, the antibody is not enabled. The possibility that an antibody may be able to bind to a native epitope but not to a modified epitope does not change the fact

that the antibody binds to the native epitope, and therefore one skilled in the art is enabled to use the antibody.

The Examiner then states that even one amino acid difference in the peptide used for the modification of the therapeutic antibody could change dramatically the affinity or binding to the antibody combining site.

As noted hereinabove, one skilled in the art can determine through routine experimentation whether a modified antibody has reduced binding to the therapeutic target, and whether there is a reduced antibody response against the modified antibody. If the modified antibody does not have reduced binding to the therapeutic target, and there is not a reduced antibody response against the modified antibody, then such modified antibody is not within the scope of the present invention. The mere fact that not every modified antibody is within the scope of the claimed invention does not mean that the present invention is not enabled.

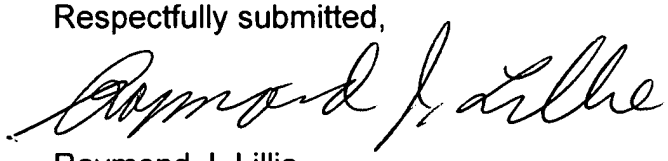
In sum, the modified antibodies of the present invention may be constructed and tested by means which are known to those skilled in the art. Thus, the specification enables one skilled in the art to make modified antibodies which have reduced binding to the therapeutic target, and have a reduced immune response against the modified antibody. In the rejection, the Examiner has confused the fact that not all modified antibodies are within the scope of the present invention with the legal standard for enablement. The present invention encompasses only modified antibodies with certain properties. Such properties can be determined readily by those skilled in the art, and the modified antibodies may be produced by techniques known to those skilled in the art. Therefore, contrary to the Examiner's allegations, the claimed invention is enabled.

It is therefore respectfully requested that the rejection under 35 U.S.C. 112, first paragraph, be reversed.

Conclusion

For the above reasons and others, this application is in condition for allowance and it is therefore respectfully requested that the rejections be reversed.

Respectfully submitted,



Raymond J. Lillie
Registration No. 31,778
Carella, Byrne, Cecchi,
Olstein, Brody & Agnello
5 Becker Farm Road
Roseland, NJ 07068-1739
Phone: (973) 994-1700
Fax: (973) 994-1744
Email: rlillie@carellabyrne.com

APPENDIX - CLAIMS ON APPEAL

1. (Rejected). A pharmaceutical comprising:

(a) a therapeutic antibody that binds to a therapeutic target, said antibody being modified with a peptide that reduces binding of the antibody to the therapeutic target, said modified antibody being effective for reducing side effects caused by the antibody and for producing a therapeutic effect by binding to the therapeutic target, wherein said antibody includes an antibody combining site that binds to the therapeutic target, and said peptide is bound to the antibody combining site of said antibody; and (b) a pharmaceutical carrier.

2-5 Cancelled.

6. (Rejected). The pharmaceutical of Claim 1 wherein the avidity of the modified antibody combined with the peptide is at least 4-fold less than the avidity of the unmodified antibody and no more than 100-fold less.

7. (Rejected). The pharmaceutical of Claim 6 wherein the antibody is an aglycosylated antibody.

8. (Rejected). The pharmaceutical of Claim 7 wherein only one of the chains of the antibody has a peptide linked thereto that binds to the antibody combining site.

9. (Rejected). The pharmaceutical of Claim 1 wherein the peptide is reversibly bound to the antibody combining site, whereby the amount of antibody that binds to the target increases as the peptide is displaced from the antibody binding site.

10. (Rejected). The pharmaceutical of Claim 9 wherein the peptide bound to the antibody combining site is also linked to the antibody.

11. Cancelled.

12. (Rejected). The pharmaceutical of Claim 10 wherein the Fc portion of the antibody is aglycosylated.

13. (Rejected). The pharmaceutical of Claim 10 wherein binding of the antibody to the Fc receptor is essentially eliminated.

14. (Rejected). The pharmaceutical of Claim 10 wherein the antibody is a non-human antibody.

15. (Rejected). The pharmaceutical of Claim 10 wherein the antibody is a chimeric antibody.

16. (Withdrawn) A process for treating a mammal, comprising administering to a mammal the pharmaceutical of Claim 1 in an amount effective to both treat the mammal and reduce side effects against the protein.

17. (Rejected) The pharmaceutical of Claim 10 wherein the antibody is a humanized antibody.

EVIDENCE APPENDIX

None

RELATED PROCEEDINGS APPENDIX

Not Applicable

#398698 v1